Bortezomib Maintenance Therapy- 14 day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Maintenance treatment for patients with high risk multiple myeloma.	C90	00435a	N/A

* This is for post 2012 indications only.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Bortezomib is administered once every 14 days for 2 years or until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Cycle
1	Bortezomib	1.3mg/m^2	[a,b] SC (abdomen or thigh)	Every 14 days
[a]Note: In individual cases where approved by consultant, bortezomib may be administered as IV bolus over 3-5 seconds through a peripheral or central intravenous catheter followed by a flush with 0.9% NaCl. Note the concentration of bortezomib solution should be 1mg/mL when administered via the IV route.				
[b]The solution should be injected subcutaneously (SC), at a 45-90^0 angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered SC or a switch to intravenous injection is recommended.				
Bortezomib is a proteasome inhibitor and is neurotoxic. Refer to **NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer**. Here				

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron or any of the excipients
- Pregnancy

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Blood pressure, blood glucose (patients on oral hypoglycaemics)
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV

Regular tests:

- FBC; monitor platelet count prior to each cycle
- Renal, liver and bone profile
- Blood pressure, blood glucose if being treated with oral hypoglycaemics

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Bortezomib therapy should be withheld when the platelet count is < 25 x 10^9 /L

Haematological:

Table 1: Dose modification of bortezomib based on haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Bortezomib Dose
≥ 0.5	**and**	**≥ 30**	100% dose
< 0.5	**or**	**<30**	Consider delay until recovery checking FBC weekly; reduce dose to 1.0 mg/m^2
Reoccurrence of < 0.5	**or**	**Reoccurrence of < 30**	Consider delay until recovery checking FBC weekly; further reduce dose to 0.7 mg/m^2

Renal and Hepatic Impairment:

Table 2: Recommended dose modification for renal or hepatic impairment

Drug	Renal impairment	Hepatic impairment			
		Grade of Hepatic Impairment*	**Bilirubin Level****	**(AST) Levels****	**Modification of starting dose**
Bortezomib	No dose adjustment is needed. Haemodialysis: no dose adjustment is needed, administer after haemodialysis.	Mild	≤1 x ULN	> ULN	None
			>1-1.5xULN	Any	None
		Moderate	>1.5-3xULN	Any	Reduce dose to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability.
		Severe	>3xULN	Any	
Renal dose modifications - Giraud et al 2023. Hepatic dose modifications - SmPC					

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe)

**ULN = Upper Limit Normal

Neuropathic pain and/or peripheral neuropathy:

Table 3: Recommended dose modifications for bortezomib-related neuropathy

Severity of neuropathy	Dose Modification
Grade 1(asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL))	Reduce dose to 1 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m^2
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue treatment

Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

Dose reductions for other toxicities:

Table 4: Dose modification schedule of bortezomib based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Grade ≥ 3 Non-haematological toxicity		Withhold treatment until symptoms of the toxicity have resolved. Treatment may be re-initiated at a 25% reduced dose (1.3mg/m^2 reduced to 1.0mg/m^2; 1.0mg/m^2 reduced to 0.7mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk
New or worsening pulmonary symptoms (e.g. cough, dyspnoea)		Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.
Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue bortezomib	

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

SUPPORTIVE CARE:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here:

EMETOGENIC POTENTIAL: Low (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS: Not usually required. Ensure patient remains well hydrated during treatment

OTHER SUPPORTIVE CARE:

- Bisphosphonates should be considered in all patients with myeloma related bone disease
- Consider the use of a H_2 antagonist or proton pump inhibitor if appropriate in patients receiving dexamethasone therapy **(Refer to local policy)**
- Consider PJP prophylaxis **(Refer to local policy)**
- Consider low dose anti-viral prophylaxis **(Refer to local policy)**

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Neben K, Lokhorst HM et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood 2012;119(4):940-8.
2. Sonneveld P, Schmidt-Wolf IG et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012;30(24):2946.
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. VELCADE ®Summary of Product Characteristics. Accessed March 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	10/10/2018		Prof. Ezzat Elhassadi
2	12/05/2021	Regimen review Updated wording regarding management of hepatitis B reactivation	Prof. Ezzat Elhassadi

3	29/07/2024	Updated regular testing section. Updated renal dose modifications section to align to Giraud et al 2023. Adverse Effects, Regimen Specific Complications and Drug Interactions sections removed and replaced with standard wording.	Prof. Ezzat Elhassadi

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of bortezomib in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.